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How to Teach the Topic of Acute Myelogenous Leukemia: Recommendations for Achieving Curricular Milestones

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Abstract

In the Next Accreditation System, the evaluation of trainees and programs has changed such that there are specific achievement goals and outcomes for both. The distinct concepts that the trainee needs to know in the epidemiology, clinical presentation, evaluation and management of acute myelogenous leukemia allow for adapting these achievement goals into a specific set of skills that match the major curricular milestones in Hematology/Oncology. We intend to demonstrate how knowledge and management skills acquired in the study of AML may be utilized to assess several domains of knowledge and skills of the trainee in the current accreditation system.

Keywords: Acute myelogenous leukemia; Curricular milestones; Hematology

Introduction

Although there is an evolving literature devoted to novel methods of teaching Generation Y learners in the environments of medical school and post-graduate training, the objectives of teaching in a medical environment remain the same as they were a hundred years ago: to communicate an idea, or to develop a procedural or technical skill. For the most part, in Hematology, our major objectives center on the introduction of new concepts in pathophysiology, diagnostic evaluation, and pharmacology, and how these relate to clinical situations. In the Next Accreditation System [1] the evaluation of trainees and programs has changed, such that there are specific achievement goals and outcomes for both.

Important Concepts Regarding Diagnosis, Evaluation, and Management of Acute Myelogenous Leukemia

At the start of each rotation on the acute leukemia service, it is important to set expectations for the trainees. It is understood that performance expectations are graduated, depending upon the level of training of each member of the team. When teaching the basics about acute myelogenous leukemia, it is good to start with a didactic set of principles regarding disease biology and therapy. If the conversation is interactive it is possible to ascertain fund of knowledge in malignant hematology (MK1b in the Hematology/Oncology Curricular Milestones, summarized in [2]. Many teachers prefer to start with a case. This case-based method has been used for years, and probably first gained acceptance as a means to teach Medical Ethics. The idea was 'you show me the case, and I'll teach you the ethical response.' Of course, this is not at all the history of teaching deontological, or for that matter, utilitarian Ethics. This branch of philosophy has a didactic set of principles, but when it became too difficult to teach the principles, it was easier to teach from a case. This is the way some people learn foreign languages as well, by the situation, rather than with a framework. That system can result in critical information voids. We believe that a structured learning system that later relates to the specific results in greater adaptability. For instance, it is certainly easier to develop a general set of objectives for a presentation of AML. There are distinct concepts that the student or fellow needs to know, namely the epidemiology of AML; the relationship of AML to antecedent hematological disturbances, environmental and occupational exposures, the use of prior cytotoxic chemotherapy and/or radiation; and how these antecedents predict for distinct morphologic, cytogenetic, and molecular subtypes of AML. This addresses MK2 that requires a trainee to demonstrate knowledge of genetic, genomic, and molecular features of cancer. The presentation may be preceded, for certain audiences, by considering the peripheral blood smear of the typical patient with AML (PC4b1), then discussing normal function of the bone marrow. Just as an automobile factory makes many types of vehicles, the marrow is responsible for the production of a diverse set of functional blood cells. During the discussion the concepts are reinforced, through direct questioning of the audience to determine the level of understanding of genotypic differences among phenotypic similarities. The next major point is to communicate the distinctions among AML subtypes as they relate to the epidemiology that we just discussed the accompanying morphology, and the dominant clonal cytogenetic and molecular patterns that describe AML sub-types as we know them today. Now this effort to make coherent that which may seem incoherent to the listener is made all the easier due to the static treatment landscape over the last forty years that has allowed the assignment of prognosis to the very different subtypes of AML. The factory analogy can be continued by stating that generally, in AML, the diverse factories shut down, and that only one factory remains on-line, producing cars and trucks that are missing engine-blocks or drive-shafts, rendering them useless, halting all transit of important substances, in the case of the marrow, through the bloodstream, a state incompatible with long survival.

What it takes to Distinguish AML Subtypes

Distinguishing AML by the dominant clonal cytogenetic or molecular pattern doesn't address how the abnormalities occur, but does introduce the concepts of cytogenetic and molecular diagnostics as a distinct way to classify cancers beyond the morphology or perceived site of origin3. We further discuss the refinements in risk stratification conferred by recurrent single-gene mutations as they have been identified [4]. This provides an opportunity to speak about the clinically distinct acute promyelocytic leukemia, its unusual epidemiology, its distinct cytogenetics, and the molecular features that today do inform therapy5. Other refinements in risk stratification are useful today, only for prognostication, or may contribute in some way not yet completely confirmed, in the recommendation for one form of therapy over another. For fellows, we present our bias that the standard evaluation of AML must consist, at the minimum, of flow cytometry, immunohistochemistry, FISH for common abnormalities such at t(8;21), RUNX1-RUNX1T1; inv(16) or t(16;16); CBFB-MYH11; t(15;17); PML-RAR-alpha; t(9;11); MLL; and inv(3). Bone marrow karyotype is routine, along with molecular studies for mutations in flt3, NPM-1, Kit, and CEBP. We discuss potentially useful additional studies.

Applying the Didactic Principles to the Case and Assessing Competence in Initial Management

At this point, after having presented a framework of didactics, it is time to introduce a case to determine the level of understanding of the trainee (passive knowledge) and to elicit a treatment plan with appropriate references (active knowledge). Depending on the level of the trainee, the complexity of the case would be modified. For a fellow, an older patient with flt3-ITD-positive, normal-karyotype AML would be illustrative.

One example for fellows is of a 64 year old woman without significant past medical history who presented with abdominal pain. In the evaluation of pain, a complete blood count identified pancytopenia. The fellow would be asked what history and physical examination features would be relevant (PC1), and about specific elements regarding the initial diagnostic work-up (PC2a). A bone marrow aspirate and biopsy confirmed the appearance of an acute myeloid leukemia expressing CD13, CD15, CD19, CD33, CD34,CD36 (partial), CD38, CD45 (dim), CD71 (partial), CD79a(partial), CD117, HLA-DR, Tdt (partial) and aberrant expression of CD7. The fellow would then be asked how to apply this information to risk factors established by large cooperative groups and place the meaning of the aberrant lymphoid antigen expression. The response would inform whether the fellow is able to critically read scientific literature (MK3).

In this case, cytogenetic analysis identified normal karyotype, a finding that is present in 30-40% of adults with newly diagnosed AML. The trainee would be asked what additional molecular studies should be requested (MK2); this case had presence of a flt3 ITD [6,7]. Allelic ratio was not done, and is not part of the conventional workup in most institutions, but one can speak to its potential meaning. At this juncture, the discussion should include availability of clinical trials (PC2e) for this case, and whether additional studies (other mutation analysis, such as NPM1, Kit, and CEBP) would be required. These studies typically take two weeks to return, and are not available to inform decisions about induction therapy. Even were these studies available, presently, outside of a clinical trial, there is no evidence that the addition of a kinase inhibitor with conventional chemotherapy would improve the likelihood of achieving complete remission, or confer survival benefit after whatever therapy. However, at some time in the future, this may change.

The fellow would then be asked to formulate the plan for induction chemotherapy (PC2a and PC4b2), about the prognostic value of both pretreatment cytogenetics and molecular analysis (MK2), and the need for reflex testing by hematopathology (PC2c) since the molecular pathology results contribute to the way we think clinically about AML. We can also speak about clinical factors associated with high-risk AML, such as comorbid medical conditions (PC2a) and advanced age (PC2f), and when consultation from other specialties is indicated (PC5).

The case also permits discussing about the meaning of complete remission, the place for minimal-residual-disease testing, and the potential for consolidative therapies to alter survival8 (PC2c). Older patients are at a higher risk for treatment-related toxicity, but also tend to have disease more likely to recur. These toxicities must be appreciated (PC2d) so that a discussion about adjunctive therapies, such as hematopoietic growth factors, prophylactic antimicrobials, and lower thresholds for transfusion support (PC2g) can occur. These treatments have not been demonstrated to significantly improve outcome, even in the high-risk older patient, but do provide ample opportunity for discussions regarding palliative care (PC2k) and potential side-effects and toxicities (PC2h).

Allogeneic Transplantation: Assessing Competence in Management of High-Risk AML

The case of flt3-mutated AML in an older patient will lead to discussion of allogeneic transplantation, something required of fellows as a core competency to demonstrate knowledge of the principles of, and indications for stem cell transplantation (PC2i). Identifying a high risk of relapse may lead to earlier use of allogeneic transplant, but adverse disease biology still confers increased risk of relapse despite transplant [9] (MK1b). Retrospective studies suggest that the adoptive immune therapy achieved with allogeneic transplantation offers a survival advantage for patients with high-risk AML, typically demonstrated by donor vs. no-donor comparative trials. Notwithstanding some disagreements, most consider allogeneic transplantation as indicated for the management of high-risk AML, but its use among those with adverse clinical features, such as older age, is still controversial [10,11].

It is generally easier to accomplish a determination of the educational intervention by direct assessment. This may be accomplished by asking the fellow to give a presentation on donor versus no-donor comparisons of management of high-risk AML in first remission, the flaws of such studies, and interpretations. It may involve a presentation of kinase inhibitors under investigation and the potential ways to utilize these drugs in clinical practice [12,13]. Medicine tends to force a disease narrative on the learner, and the literature doesn't allow for much personal or affective connection with the educator, but a bedside presentation using general, review articles, may allow for an assessment of what the trainee has been able to learn about conventional therapies, allogeneic transplantation and drug development as they pertain to AML. This bedside presentation would allow assessment of fellow performance regarding MK1, MK2, Prof 3 and ICS-1.

The Teaching Perspective

The major advantage for oral presentations, in lectures, on rounds, and at the bedside, is that the human component, the affective connection, is there for all to see and hear. Success in direct communication takes advantage of that affective connection. Successful teachers, and their trainees, therefore, should eventually know the topic sufficiently well to speak without props especially slides. Direct communication hinges on engaging the learner. Engaging the audience means 1) establishing the distinctiveness of the presentation at the beginning, 2) making the most general statements at first, and making the most arcane statement in the middle, and 3) clarifying the meaning of studies at the end of the presentation. Highlighting certain results, minimizing conclusions, and concluding early generally yield the most favorable reviews of formal lectures, and the same thing occurs at the bedside. Making clear the fewest number of conclusions produces the best retention of what we really wanted to communicate in the first place- biologic features of AML, the impact of these features in defining risk, minimal-residual disease testing, the role of transplant as consolidation, and the place for new drugs in the treatment paradigm.

If this rigorous and interactive approach is followed with each case on the acute leukemia service, supervising physicians can assess competence of fellows in many of the Hematology/Oncology curricular milestones, as has been highlighted in the text. As shown in abbreviated form in, this can be applied to learners at multiple levels. Over time, one could assess development of independence (PC3), experience with negotiating and facilitating transitions of care (PC2m, SBP4), performance in chart documentation (ICS3) and performance and communication in the inter-professional team environment (SBP1, ICS2). Thus, clinical performance can be accurately assessed in multiple domains. Further, with minimal changes, quality improvement exercises and discussions regarding systems-based factors that impact the patients on the service could be added. This indicates that a rotation on the Acute Leukemia Service is a critical part of fellowship training in Hematology.

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